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(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST

#### (57) Abstract

A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9\alpha,11\alphasubstituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.

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# METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY STEROIDAL ALDOSTERONE ANTAGONIST

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#### Field of the Invention

Therapeutic methods are described for treatment of cardiofibrosis and cardiac hypertrophy. Of particular interest are therapies using an epoxy-containing steroidal aldosterone receptor antagonist compound such as epoxymexrenone in combination with an angiotensin II receptor antagonist compound.

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#### Background of the Invention .

Myocardial (or cardiac) failure, whether a consequence of a previous myocardial infarction, heart disease associated with hypertension, or primary cardiomyopathy, is a major health problem of worldwide proportions. The incidence of symptomatic heart failure has risen steadily over the past several decades.

In clinical terms, decompensated cardiac failure

consists of a constellation of signs and symptoms that
arises from congested organs and hypoperfused tissues to
form the congestive heart failure (CHF) syndrome.

Congestion is caused largely by increased venous pressure
and by inadequate sodium (Na') excretion, relative to dietary

Na' intake, and is importantly related to circulating levels
of aldosterone (ALDO). An abnormal retention of Na' occurs
via tubular epithelial cells throughout the nephron,
including the later portion of the distal tubule and
cortical collecting ducts, where ALDO receptor sites are

present.

ALDO is the body's most potent mineralocorticoid hormone. As connoted by the term mineralocorticoid, this

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steroid hormone has mineral-regulating activity. It promotes Na+ reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive 5 tissues. ALDO regulates Na<sup>+</sup> and water resorption at the expense of potassium (K') and magnesium (Mg2+) excretion.

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ALDO can also provoke responses in nonepithelial cells. Elicited by a chronic elevation in plasma ALDO level 10 that is inappropriate relative to dietary Na intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

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Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as nonrenin-dependent factors (such as K<sup>\*</sup>, ACTH) that promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine its plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

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The renin-angiotensin-aldosterone system (RAAS) is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension. Activation of the renin-angiotensinaldosterone system begins with renin secretion from the juxtaglomerular cells in the kidney and culminates in the formation of angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological 35 effects such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic

effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II binding at its receptors is a viable approach to inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such peptidic compounds are of limited use due to their lack of oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, early descriptions of such non-peptidic compounds include the 20 sodium salt of 2-n-butyl-4-chloro-1-(2chlorobenzyl)imidazole-5-acetic acid which has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [P. C. Wong et al, J. Pharmacol, Exp. Ther., 247(1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-25 (2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [A. T. Chiu et al, European J. Pharmacol., 157, 31-21 30 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol, Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-35 tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant

decrease in mean arterial blood pressure in conscious hypertensive rats. Other families of non-peptidic angiotensin II antagonists have been characterized by molecules having a biphenylmethyl moiety attached to a heterocyclic moiety. For example, EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, 10 namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4substituted-4H-1,2,4-triazoles, including the compound 3,5dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4triazole. U.S. Patent No. 4,880,804 to Carini et al describes a family of biphenylmethylbenzimidazole compounds as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

20 Many aldosterone receptor blocking drugs are known. For example, spironolactone is a drug which acts at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium 25 transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosteronerelated diseases such as liver cirrhosis and congestive 30 heart failure [F.J. Saunders et al, Aldactone; Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day) were administered to a spironolactone-intolerant 35 patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug, 1986)]. It has been recognized that development of

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myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to 5 excessive collagen deposition [D. Klug et al, Am. J. <u>Cardiol.</u>, <u>71</u> (3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G. Brilla et al, J. Mol. Cell. 10 Cardiol., 25(5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 15 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)1.

Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

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Moreover, although ACE inhibitors effectively block the formation of angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, <u>J. Endocrinol.</u>, <u>91</u>, 457-465 (1981)]. A similar effect has been observed for patients 35 with myocardial infarction receiving zofenopril [C. Borghi et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. This phenomenon has been termed "aldosterone escape".

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Another series of steroidal-type aldosterone receptor antagonists is exemplified by epoxy-containing spironolactone derivatives. For example, U.S. Patent No. 4,559,332 issued to Grob et al describes  $9\alpha$ ,11 $\alpha$ -epoxy-containing spironolactone derivatives as aldosterone antagonists useful as diuretics. These  $9\alpha$ ,11 $\alpha$ -epoxy steroids have been evaluated for endocrine effects in comparison to spironolactone [M. de Gasparo et al, J. Pharm. Exp. Ther., 240(2), 650-656 (1987)].

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Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and that aldosterone levels increase as CHF progresses from activation of the Renin-Angiontensin-Aldosterone System (RAAS). Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. <u>Cardiol.</u>, 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of captopril and spironolactone was administered and found effective to control refractory CHF without serious incidents of hyperkalemia [U. Dahlstrom et al, Am. <u>J. Cardiol.</u>, <u>71</u>, 29A-33A (21 Jan 1993)]. Spironolactone coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure [A.A. van Vliet et al, Am. J. Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to

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determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)].

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Combinations of an angiotensin II receptor antagonist and aldosterone receptor antagonist, are known. For example, PCT Application No. US91/09362 published 25 June 1992 describes treatment of hypertension using a combination of an imidazole-containing angiotensin II antagonist compound and a diuretic such as spironolactone.

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### Summary of the Invention

A therapeutic method for treating or preventing the progression of cardiofibrosis or cardiac hypertrophy is provided by a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist.

10 The phrase "angiotensin II receptor antagonist" is intended to embrace one or more compounds or agents having the ability to interact with a receptor site located on various human body tissues, which site is a receptor having a relatively high affinity for angiotensin II and which 15 receptor site is associated with mediating one or more biological functions or events such as vasoconstriction or vasorelaxation, kidney-mediated sodium and fluid retention, sympathetic nervous system activity, and in modulating secretion of various substances such as aldosterone, vasopressin and renin, to lower blood pressure in a subject 20 susceptible to or afflicted with elevated blood pressure. Interactions of such angiotensin II receptor antagonist with this receptor site may be characterized as being either "competitive" (i.e., "surmountable") or as being "insurmountable". These terms, "competitive" and 25 "insurmountable", characterize the relative rates, faster for the former term and slower for the latter term, at which the antagonist compound dissociates from binding with the receptor site.

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The phrase "epoxy-steroidal aldosterone receptor antagonist" is intended to embrace one or more agents or compounds characterized by a steroid-type nucleus and having an epoxy moiety attached to the nucleus and which agent or compound binds to the aldosterone receptor, as a competitive inhibitor of the action of aldosterone itself at the receptor site, so as to modulate the receptor-mediated activity of aldosterone.

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The phrase "combination therapy", in defining use of an angiotensin II antagonist and an epoxy-steroidal aldosterone receptor antagonist, is intended to embrace administration of each antagonist in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended to embrace co-administration of the antagonist agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each antagonist agent.

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The phrase "therapeutically-effective" is intended to qualify the amount of each antagonist agent for use in the combination therapy which will improve cardiac sufficiency by reducing or preventing the progression of myocardial fibrosis or cardiac hypertrophy.

Another combination therapy of interest would consist essentially of three active agents, namely, an AII antagonist, an aldosterone receptor antagonist agent and a diuretic.

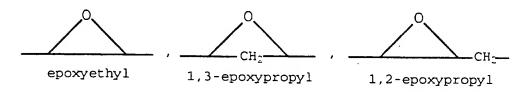
ALDO antagonist agent, the agents would be used in combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of the AII antagonist agent to the aldosterone receptor antagonist agent. A preferred range of these two agents (AII antagonist-to-ALDO antagonist) would be from about one-to-one to about fifteen-to-one, while a more preferred range would be from about one-to-one to about five-to-one, depending ultimately on the selection of the AII antagonist and ALDO antagonist. The diuretic agent may be present in a ratio range of 0.1-to-one to about ten to one (AII antagonist to diuretic).

#### Detailed Description of the Invention

Epoxy-steroidal aldosterone receptor antagonist compounds suitable for use in the combination therapy consist of these compounds having a steroidal nucleus substituted with an epoxy-type moiety. The term "epoxytype" moiety is intended to embrace any moiety characterized in having an oxygen atom as a bridge between two carbon atoms, examples of which include the following moieties:

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The term "steroidal", as used in the phrase "epoxysteroidal", denotes a nucleus provided by a cyclopentenophenanthrene moiety, having the conventional "A", "B", "C" and "D" rings. The epoxy-type moiety may be attached to the cyclopentenophenanthrene nucleus at any attachable or substitutable positions, that is, fused to one of the rings of the steroidal nucleus or the moiety may be 20 substituted on a ring member of the ring system. The phrase "epoxy-steroidal" is intended to embrace a steroidal nucleus having one or a plurality of epoxy-type moieties attached thereto.

25 Epoxy-steroidal aldosterone receptor antagonists suitable for use in combination therapy include a family of compounds having an epoxy moiety fused to the "C" ring of the steroidal nucleus. Especially preferred are 20spiroxane compounds characterized by the presence of a 30  $9\alpha$ ,  $11\alpha$ -substituted epoxy moiety. Table I, below, describes a series of  $9\alpha$ ,  $11\alpha$ -epoxy-steroidal compounds which may be used in the combination therapy. These epoxy steroids may be prepared by procedures described in U.S. Patent No. 4,559,332 to Grob et al issued 17 December 1985.

TABLE I: Aldosterone Receptor Antagonist

Structure	
Compound #	

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Name

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, methyl ester,

 $(7\alpha, 11.\alpha., 17\alpha)$  -

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Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester,  $(7\alpha,11\alpha,17\alpha)$ -

TABLE I: Aldosterone Receptor Antagonist

Compound # Structure

Name

3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ -lactone,(6 $\beta$ ,7 $\beta$ ,11 $\beta$ ,17 $\beta$ )-

Pregn-4-ene-7,21-dicarboxylic acid,9,11epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester,
monopotassium salt,(7a,11a,17a)-

Aldosterone Receptor Antagonist TABLE I:

> Structure Compound #

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Name

17-hydroxy-3-oxo-,7-methyl ester, monopotassium Pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxysalt, (7a,11a,17a)-

carboxylic acid, 9,11-epoxy-6,7-dihydro-17-3'H-cyclopropa[6,7]pregna-1,4,6-triene-21hydroxy-3-oxo-, g-lactone(6a,7a,11.a)-

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TABLE I: Aldosterone Receptor Antagonist

Compound # Structure

Name

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxyli, acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6a,7a,11a,17a)-

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxyliacid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,monopotassium salt, (6a,7a,11a,17a)-

TABLE I: Aldosterone Receptor Antagonist

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Name

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxyliacid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,glactone, (6a,7a,11a.,17a)-

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy17-hydroxy-3-oxo-,g-lactone, ethyl ester,
(7a,11a,17a)-

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Aldosterone Receptor Antagonist TABLE I:

Name

Compound #

Structure

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, 1-methylethyl

ester, (7a,11a,17a)-

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Angiotensin II receptor antagonist compounds suitable for use in the combination therapy are described in Table II, below. Preferred compounds for use in the combination therapy may be generally characterized structurally as having two portions. A first portion constitutes a mono-aryl-alkyl moiety, or a bi-aryl-alkyl moiety, or a mono-heteroaryl-alkyl moiety, or a biheteroaryl-alkyl moiety. A second portion constitutes a heterocyclic moiety or an open chain hetero-atom-containing moiety. .

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Typically, the first-portion mono/biaryl/heteroaryl-alkyl moiety is attached to the second portion heterocyclic/open-chain moiety through the alkyl group of the mono/bi-aryl/heteroaryl-alkyl moiety to any substitutable position on the heterocyclic/open-chain moiety second portion. Suitable first-portion mono/biaryl/heteroaryl-alkyl moieties are defined by any of the various moieties listed under Formula I:

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Ar-Alk-L Ar-L-Ar-Alk-L Het-L-Ar-Alk-L Het-L-Het-Alk-L (I) Ar-L-Het-Alk-L Het-L-Alk-L

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wherein the abbreviated notation used in the moieties of Formula I is defined as follows:

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"Ar" means a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being typically fully unsaturated but which also may be partially or fully saturated. "Phenyl" radical 35 most typically exemplifies "Ar".

"Het" means a monocyclic or bicyclic fused ring

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system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members.

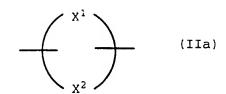
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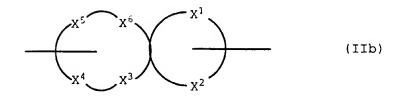
"Alk" means an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms. Typically, "Alk" means "methylene", i.e., -CH2-.

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"L" designates a single bond or a bivalent linker moiety selected from carbon, oxygen and sulfur. When "L" is carbon, such carbon has two hydrido atoms attached thereto.

Suitable second-portion heterocyclic moieties of the angiotensin II antagonist compounds, for use in the combination therapy, are defined by any of the various moieties listed under Formula IIa or IIb:





wherein each of X<sup>1</sup> through X<sup>6</sup> is selected from -CH=, -CH<sub>2</sub>-,

-N=, -NH-, 0, and S, with the proviso that at least one of
X<sup>1</sup> through X<sup>6</sup> in each of Formula IIa and Formula IIb must be
a hetero atom. The heterocyclic moiety of Formula IIa or
IIb may be attached through a bond from any ring member of
the Formula IIa or IIb heterocyclic moiety having a

substitutable or a bond-forming position.

Examples of monocyclic heterocyclic moieties of Formula IIa include thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, 15 pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 20 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl, 25 piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-

oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl,

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1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

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Examples of bicyclic heterocyclic moieties of

Formula IIb include benzo[b]thienyl, isobenzofuranyl,
chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl,
purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl,
naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl,
pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl,

2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl,
1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl,
pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl,
cyclopenta[b]pyranyl, 4H-[1,3]oxathiolo-[5,4-b]pyrrolyl,
thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and
4H-1,3-dioxolo[4,5-d]imidazolyl.

The angiotensin II receptor antagonist compounds, as provided by the first-and-second-portion moieties of Formula I and II, are further characterized by an acidic moiety attached to either of said first-and-second-portion moieties. Preferably this acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

 $-U_nA$  (III)

20

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wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the  $-U_nA$ 

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moiety, is intended to embrace chemical groups which, when attached to any substitutable position of the Formula I-IIa/b moiety, confers acidic character to the compound of Formula I-IIa/b. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I-IIa/b to be a proton donor in the presence of a protonreceiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I-IIa/b has a pKa in a range from about one to about twelve. More typically, the Formula I-IIa/b compound would have a pKa in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group (-COOH). Where n is zero and A is -COOH, in the  $-U_{\mathrm{n}}A$  moiety, such carboxyl group would be attached 15 directly to one of the Formula I-IIa/b positions. The Formula I-IIa/b compound may have one -UnA moiety attached at one of the Formula I-IIa/b positions, or may have a plurality of such  $-U_DA$  moieties attached at more than one of 20 the Formula I IIa/b positions. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic 25 bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I-IIa/b may have one or more acidic protons and, therefore, may have one or more pKa values. It is preferred, however, that at least one of these pKa values of 30 the Formula I-IIa/b compound as conferred by the -UnA moiety be in a range from about two to about seven. The  $-U_nA$ moiety may be attached to one of the Formula I-IIa/b positions through any portion of the -UnA moiety which results in a Formula I-IIa/b compound being relatively 35 stable and also having a labile or acidic proton to meet the foregoing pKa criteria. For example, where the -UnA acid moiety is tetrazole, the tetrazole is typically attached at

the tetrazole ring carbon atom.

For any of the moieties embraced by Formula I and Formula II, such moieties may be substituted at any substitutable position by one or more radicals selected from 5 hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, 10 alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more 15 ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

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wherein W is oxygen atom or sulfur atom; wherein each of  $R^1$  through  $R^5$  is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl,  $YR^6$  and



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wherein Y is selected from oxygen atom and sulfur atom and R<sup>6</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl,

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arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^7$  and  $R^8$  is further independently selected from amino and amido radicals of the formula

 $R^9$   $R^{11}$  and  $N^{-NC-R^{13}}$ 

5

wherein W is oxygen atom or sulfur atom; wherein each of  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  is independently selected from hydrido, alkyl, cycloalkyl, 10 cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of  $\mathbb{R}^2$  and  $\mathbb{R}^3$  taken together and each of  $\mathbb{R}^4$  and R<sup>5</sup> taken together may form a heterocyclic group having five 15 to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of  $R^2$  and  $R^3$  taken together and each of  $R^7$  and  $R^8$  taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more 25 hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The combination therapy of the invention would be useful in treating myocardial fibrosis or cardiac hypertrophy, particularly left ventricular hypertrophy. The combination therapy would also be useful with adjunctive therapies. For example, the combination therapy may be used in combination with other drugs, such as a diuretic, to aid

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in treatment of hypertension.

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Table II, below, contains description of angiotensin II antagonist compounds which may be used in the combination therapy. Associated with each compound listed in Table II is a published patent document describing the chemical preparation of the angiotensin II antagonist compound as well as the biological properties of such compound. The content of each of these patent documents is incorporated herein by reference.

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

5

Structure

Source

WO #91/17148 pub. 14 Nov 91

WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

Z-CH2

MO #91/17148 pub. 14 Nov 91

8

WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

13

WO =91/17148 pub. 14 Nov 91

14

WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO =91,17148 pub. 14 Nov 91

WO #91/17148 pub. 14 Nov 91

# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

Compound # "...

Structure

Source

WO =91/17148 pub. 14 Nov 91

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WO #91/17148 pub. 14 Nov 91

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# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

WO #91/17148 pub. 14 Nov 91

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

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# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

<del>1</del>3

WO #91/17148 pub. 14 Nov 91

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

46

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO =91/17148 pub. 14 Nov 91

WO #91/17148 pub. 14 Nov 91

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

Ξ2

WO #91/17148 pub. 14 Mov 91

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

55

WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

61

WO #71/17148 pub. 14 Nov 91

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

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Structure

Source

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO =91/17148 pub. 14 Nov 91

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WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/17148 pub. 14 Nov 91

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/18888

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WO #91/18888 pub.

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

81

WO #91/18888 pub.

82

WO #91/18888 pub.

83

WO #91/18888 . duq

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

84

WO #91/18888 pub.

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WO #91/18888 pub.

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/18888 pub.

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WO #91/18888 pub.

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

90

WO #91/18888 pub.

91

WO #91/18888 pub.

92

WO #91/18888

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

93

WO #91/18888 pub.

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WO #91/18888 pub.

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#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/18888 pub.

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #91/18888 pub.

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

102

WO #91/18888 pub.

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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TABLE II: Angiotensin II Antagonists

Compound #

Structure .

Source

108

WO #91/19715 pub. 26 Dec 91

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WO #91/19715 pub. 26 Dec 91

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #91/19715 pub. 26 Dec 91

112 
$$N = N$$
 $N = N$ 
 $N = N$ 

WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #91/19715 pub. 26 Dec 91

WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO ≑91/19715 pub. 26 Dec 91

WO #91/19715 pub. 26 Dec 91

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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#### TABLE II: Angiotensin II Antagonists

Compound #

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Structure

Source

WO #92/05161 pub. 2 Apr 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

129

WO #92/05161 pub. 2 Apr 92

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WO #92/05161 pub. 2 Apr 92

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WO #92/05161 pub. 2 Apr 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/07834 pub. 14 May 92

WO #92/07834 pub. 14 May 92

WO #92/07834 pub. 14 May 92

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/07834 pub. 14 May 92

N O CH2

WO #92/07834 pub. 14 May 92

WO #92/07834 pub. 14 May 92

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WO 96/40255 PCT/US96/08709

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# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/07834 pub. 14 May 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

141

WO #92/11255 pub. 9 Jul 921

142

WO #92/11255 pub. 9 Jul 92

WO #92/11255 pub. 9 Jul 92

## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/15577 pub. 17 Sep 92

WO #92/15577 pub. 17 Sep 92

WO #92/15577 pub. 17 Sep 92 WO 96/40255 PCT/US96/08709

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#### TABLE II: Angiotensin II Antagonists

Compound #

152

Structure

Source

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/16523 pub. 1 Oct 92

WO #92/16523 pub. 1 Oct 92

WO #92/16523 pub. 1 Oct 92

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#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #92/16523 pub. 1 Oct 92

WO 96/40255 PCT/US96/08709

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### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

CH<sub>2</sub>
N-N
N-N

WO 96/40255

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/16523 pub. 1 Oct 92

WO #92/16523 pub. 1 Oct 92

# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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TABLE II: Angiotensin II Antagonists

Compound #

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Structure

Source

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #92/16523 pub. 1 Oct 92

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/16523 pub. 1 Oct 92

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#### TABLE II: Angiotensin II Antagonists

OC:H-

Compound #

Structure

Source

WO #92/16523 pub. 1 Oct 92

WO #92/16523 pub. 1 Oct 92

WO #92/16523 pub. 1 Oct 92

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/16523 pub. 1 Oct 92

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WO #92/16523 pub. 1 Oct 92

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #92/17469 pub. 15 Oct 92

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WO #92/17469 pub. 15 Oct 92

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #92/17469 pub. 15 Oct 92

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WO #92/17469 pub. 15 Oct 92

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### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/17469 pub. 15 Oct 92

WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #92/17469 pub. 15 Oct 92

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### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/17469 pub. 15 Oct 92

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #92/17469 pub. 15 Oct 92

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WO #92/17469 pub. 15 Oct 92

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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WO #92/17469 pub. 15 Oct 92

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/17469 pub. 15 Oct 92

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

213

₩O #92/17469 pub. 15 Oct 92

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WO #92/17469 pub. 15 Oct 92

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### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/17469 pub. 15 Oct 92

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#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/17469 pub. 15 Oct 92

WO #92/17469 pub. 15 Oct 92

# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

223

WO #92/17469 pub. 15 Oct 92

TABLE II: Angiotensin II Antagonists

Compound #

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Structure

Source

WO #92/17469 pub. 15 Oct 92

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# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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# TABLE II: Angiotensin II Antagonists

Compound #

241

Structure

Source

WO #92/18092 pub. 29 Oct 92

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WO #92/18092 pub. 29 Oct 92

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source ·

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245

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### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/18092 pub. 29 Oct 92

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### TABLE II: Angiotensin II Antagonists

Compound #

Structure

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

254

110

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/18092 pub. 29 Oct 92

WO #92/18092. pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

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WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

265

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#### TABLE II: Angiotensin II Antagonists

Compound #

268

Structure

Source

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

WO #92/18092 pub. 29 Oct 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #92/18092 pub. 29 Oct 92

PCT/US95/02156 filed 8 Mar 94

PCT/US94/02156 filed 8 Mar 94

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

PCT/US94/02156 filed 8 Mar 94

PCT/US94/02156 filed 8 Mar 94

PCT/US94/02156 filed 8 Mar 94

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

PCT/US94/02156 filed 8 Mar 94

PCT/US94/02156 filed 8 Mar 94

PCT/US94/02156 filed 8 Mar 94

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO #91/17148 pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

· Compound #

Structure .

Source

281

EP =475,206 pub. 18 Mar 92

282

WO #93/18035 pub. 16 Sep 93

283

WO #93/17628 pub. 16 Sep 93

284

WO #93/17681 pub. 16 Sep 93

120

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

285

EP #513,533 pub. 19 Nov 92

286

287

EP #535,465 pub. 07 Apr 93

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

288

EP #539,713 pub. 05 May 93

289

EP #542,059 pub. 19 May 93

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СООН

EP #05 557,843 pub. 01 Sep 93

TABLE II: Angiotensin II Antagonists

Compound #

Structure

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

EP #0,569,794 pub. 18 Nov 93

EP #0,578,002 pub. 12 Jan 94

125

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

305

H<sub>2</sub>CO N CH<sub>3</sub>

EP #470,543 pub. 12 Feb 92

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TABLE II: Angiotensin II Antagonists

	Angiotensin il Antagonists	
Compound #	Structure	Source
306	H <sub>2</sub> C	∑P ≑502,314 pup. 09 Sep 92
307	CH, N, Y, C	EP #529,253 pub. 03 Mar 93
308	CH, OH	EP =543,263 pub. 26 May 93
309 ңс⊸	CH, OH	EP ≑552,765 pub. 28 Jul 93

## TABLE II: Angiotensin II Antagonists

Compound #

Structure

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

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TABLE II: Angiotensin II Antagonists

Compound #

Structure

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## TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

US =5.015.651 pub. 14 May 91

321 
$$N = CO_2H$$
  $N = N$ 

WO #92/00977 pub. 23 Jan 92

323
$$H=N, N=N$$

$$N=0$$

$$N=0$$

$$N=0$$

$$N=0$$

$$C_4H_9(n)$$

132

## TABLE II: Angiotensin II Antagonists

Compound #

Structure

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

US #5,260,325 pub. 09 Nov 93

US #5,264,581 pub. 23 Nov 93

EP #400,974 pub. 05 Dec 90

## TABLE II: Angiotensin II Antagonists

Compound #

330

Structure

Source

EP #411.766 pub. 06 Feb 91

EP #412,594 pub. 13 Feb 91

EP #419,048 pub. 27 Mar 91

331

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TABLE II: Angiotensin II Antagonists Compound # Structure Source 333 WO #91/12,001 pub. 22 Aug 91 334 WO #91/11,999 pub. 22 Aug 91 335 WO #91/11,909 pub. 22 Aug 91 336 WO #91/12,002 pub. 22 Aug 91

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TABLE II: Angiotensin II Antagonists

Compound #

338

Structure

Source

US #5,053,329 pub. 01 Oct 91

US #5,057,522 pub 15 Oct 91

WO #91/15,479 pub. 17 Oct 91

137

TABLE II: Angiotensin II Antagonists

Compound #

Structure

138

# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

343

EP #479,479 pub. 08 Apr 92

344

345

EP #481,614 pub. 22 Apr 92

139

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

346

EP =490,587 pub. 17 Jun 92

347

US #5,128,327 pub. 07 Jul 92

348

US #5,132,216 pub. 21 Jul 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

ӉС

141

# TABLE II: Angiotensin II Antagonists

Compound #

Structure

TABLE II: Angiotensin II Antagonists

Compound #

357

Structure

143

TABLE II: Angiotensin II Antagonists

Compound #

Structure

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

145

#### TABLE II: Angiotensin II Antagonists

Compound #

366

Structure

Source

EP #517,357 pub. 09 Dec 92

TABLE II: Angiotensin II Antagonists

Compound #

Structure

147

TABLE II: Angiotensin II Antagonists

Compound # Structure Source

TABLE II: Angiotensin II Antagonists

Compound #

Structure

# TABLE II: Angiotensin II Antagonists

Compound # .

376

377

Structure

Source

US #5,240,938 pub. 31 Aug 93

GB #2,264,709 pub. 08 Sep 93

GB #2,264,710 pub. 08 Sep 93

150

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

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# TABLE II: Angiotensin II Antagonists

Compound #

385

Structure

Source

US #5,276,054 pub. 04 Jan 94

386

US #5,278,068 pub. 11 Jan 94

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

154

	TABLE II:	Angiotensin II	Antagonist	s
Compound #		Structure		Source
390	N=	N. T. S.		EP =425,211 pub. 32 May 91
391		CH,		EP #427,463 pub 15 May 91
392	<sub>ң,с</sub>		р <b>н</b> Би	O #92/00068 ub. 09 Jan 92

155

	TABLE II:	Angiotensin II Antagoni	sts
Compound #		Structure	Source
393		OH N N CH,	₩O #92/02,510 pub. 20 Feb 92
394	ңс 🔷	HO	WO #92/09278 pub. 11 Jun 92
395	OH OH	J. V.H.	WO #92/10181 pub. 25 Jun 92

396 
$$CI \xrightarrow{CO_2H} N \xrightarrow{N \xrightarrow{N} N - H} C_4H_9(n)$$

TABLE II: Angiotensin II Antagonists

Compound #

Structure

397

$$N - CH_2$$
 $C_2H_5(\Pi)$ 
 $C_2H_5(\Pi)$ 
 $C_2H_5(\Pi)$ 
 $C_2H_5(\Pi)$ 

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

401 
$$\begin{array}{c} N > N \\ N - CH_2 \end{array}$$

$$C_4H_9(n)$$

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

HC.

Source

403

WO =92/10097 pub. 25 Jun 92

404

$$CF_3 \qquad N = N$$

$$CO_2H \qquad N = N$$

$$N - CH_2 \qquad N = N$$

$$C_4H_9(n)$$

405

159

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

406

407

WO #92/20651 pub. 26 Nov 92

408

WO #93/03018 pub. 18 Feb 93

### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

WO =94/00120 pub. 06 Jan 94

411 OH

EP #411,507 pub. 05 Feb 91

161

TABLE II: Angiotensin II Antagonists

Compound #

Structure

TABLE II: Angiotensin II Antagonists

Compound: #

Structure

Source

415

EP #442,473 pub. 21 Aug 91

416

EP #443,568 pub. 28 Aug 91

417

EP #459,136 pub. 04 Dec 91

163

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

EP #483,683 pub. 05 May 92

EP #518,033 pub. 16 Dec 92

EP #520,423 pub. 30 Dec 92

164

# TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

EP #546,358 pub. 16 Jun 93

WO #93/00341 pub. 07 Jan 93

WO #92/06081 pub. 16 Apr 92

423

422

165

TABLE II: Angiotensin II Antagonists

Compound #	Structure	Source
424	H,C OH FF	WO #93/00341 pub. 97 Jan 93
425	H,C ,CH,	US #5,210,204 pub. 11 May 93
426	H,C CH	EP #343,654 pub. 29 Nov 89

166

#### TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

427

WO #93/13077 pub. 08 Jul 93

428

WO #93/15734 pub. 19 Aug 93

429

US #5,246,943 pub. 21 Sep 93 The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or, as another example, one hydrido group may be attached to a carbon atom

to form a group; or, as another example, two hydrido atoms may be attached to a carbon atom to form a -CH2- group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched 10 radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. term "cycloalkyl" embraces cyclic radicals having three to 15 about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably 20 selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a 25 fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two 30 chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The term "difluoroalkyl" 35 embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched

alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carboncarbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon 10 triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl 15 portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl 20 The "alkoxy" or "alkoxyalkyl" radicals may be further substi-tuted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one 25 to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces arylsubstituted alkyl radicals such as benzyl, diphenylmethyl, 30 triphenylmethyl, phenyl-ethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "phenalkyl" and "phenylalkyl" are interchangeable. An example of "phenalkyl" is "phenethyl" which is interchangeable with "phenylethyl". 35 The terms "alkylaryl", "alkoxyaryl" and "haloaryl" denote, respectively, the substitution of one or more "alkyl",

"alkoxy" and "halo" groups, respectively, substituted on an "aryl" nucleus, such as a phenyl moiety. The terms "aryloxy" and "arylthio" denote radicals respectively, provided by aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes, respectively, divalent radicals SO and SO2. term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, 10 benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. "Lower alkanoyl" is an example of a more prefered sub-class of 15 acyl. The term "amido" denotes a radical consisting of nitrogen atom attached to a carbonyl group, which radical may be further substituted in the manner described herein. The term "monoalkylaminocarbonyl" is interchangeable with 20 "N-alkylamido". The term "dialkylaminocarbonyl" is interchangeable with "N,N-dialkylamido". The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted with alkyl groups which may optionally contain additional 25 double-bond unsaturation. The term "heteroaryl", where not otherwised defined before, embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, 30 thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member 35 carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity

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of the heteroaryl moiety is preserved after attachment. For any of the foregoing defined radicals, preferred radicals are those containing from one to about ten carbon atoms.

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Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Also included in the combination of the invention 15 are the isomeric forms of the above-described angiotensin II receptor compounds and the epoxy-steroidal aldosterone receptor compounds, including diastereoisomers, regioisomers and the pharmaceutically-acceptable salts thereof. "pharmaceutically-acceptable salts" embraces salts commonly 20 used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. 25 Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, 30 succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methansulfonic, ethanesulfonic, 35 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic,

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cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric,
malonic, galactaric and galacturonic acid. Suitable
pharmaceutically-acceptable base addition salts include
metallic salts made from aluminium, calcium, lithium,

5 magnesium, potassium, sodium and zinc or organic salts made
from N,N'-dibenzylethylenediamine, chloroprocaine, choline,
diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by
conventional means from the corresponding compound by

10 reacting, for example, the appropriate acid or base with
such compound.

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#### BIOLOGICAL EVALUATION

In order to determine the probable effectiveness of a combination therapy for treating or preventing the 5 progression of cardiofibrosis or cardiac hypertrophy, it is important to determine the potency of individual components of the combination therapy. Accordingly, in Assays "A" through "C", the angiotensin II receptor antagonist profiles 10 were determined for many of the compounds described in Table II, herein. In Assay "D", there is described a method for evaluating a combination therapy of the invention, namely, an angiotensin II receptor antagonist of Table II and an epoxy-steroidal aldosterone receptor antagonist of Table I. The efficacy of each of the individual drugs, epoxymexrenone 15 and the angiotensin II receptor blocker, and of these drugs given together at various doses, is evaluated in a rodent model. The methods and results of such assays are described below.

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#### Assay A: Antiotensin II Binding Activity

Compounds of the invention were tested for ability to bind to the smooth muscle angiotensin II receptor using a rat uterine membrane preparation. Angiotensin II (AII) was purchased from Peninsula Labs. 125I-angiotensin II (specific activity of 2200 Ci/mmol) was purchased from Du Pont-New England Nuclear. Other chemicals were obtained from Sigma Chemical Co. This assay was carried out according to the method of Douglas et al [Endocrinology, 106, 120-124 (1980)]. Rat uterine membranes were prepared from fresh tissue. All procedures were carried out at 4°C. Uteri were stripped of fat and homogenized in phosphate-buffered saline at pH 7.4 containing 5 mM EDTA. The homogenate was centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM

Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM MgCl<sub>2</sub>, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and  $125_{I-AII}$  (approximately  $10^5$  cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound 10 labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10  $\mu\text{M}$  of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor 15 binding affinity of an AII antagonist compound was indicated by the concentration (IC50) of the tested AII antagonist which gives 50% displacement of the total specifically bound  $125_{\hbox{\footnotesize I-AII}}$  from the angiotensin II  $\hbox{\footnotesize AT}_1$  receptor. Binding data were analyzed by a nonlinear least-squares curve fitting 20 program. Results are reported in Table III.

#### Assay B: In Vitro Vascular Smooth Muscle-Response for AII

25 The compounds of the invention were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled

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with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (mM): 130 NaCl, 15 NaHC03, 15 KCl, 1.2 NaH2P04, 1.2 MgS04, 2.5 CaCl2, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was 5 placed on the rings. Angiotensin II concentration-response curves were then recorded (3  $\times$  10<sup>-10</sup> to 1  $\times$  10<sup>-5</sup> M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of 10 AII. Aorta rings were exposed to the test antagonist at  $10^-$ 5 M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of 15 the test antagonist. The effectiveness of the test compound was expressed in terms of pA2 values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The pA2 value is the concentration of the antagonist which increases the EC50 value for AII by a factor of two. Each test antagonist was evaluated in aorta 20 rings from two rabbits. Results are reported in Table III.

# Assav C: In Vivo Intragastric Pressor Assav Response for All Antagonists

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Male Sprague-Dawley rats weighing 225-300 grams were anesthetized with methohexital (30 mg/kg, i.p.) and catheters were implanted into the femoral artery and vein. The catheters were tunneled subcutaneously to exit dorsally, posterior to the head and between the scapulae. The catheters were filled with heparin (1000 units/ml of saline). The rats were returned to their cage and allowed regular rat chow and water ad libitum. After full recovery from surgery (3-4 days), rats were placed in Lucite holders and the arterial line was connected to a pressure transducer. Arterial pressure was recorded on a Gould polygraph (mmHg). Angiotensin II was administered as a 30

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ng/kg bolus via the venous catheter delivered in a 50  $\mu l$ volume with a 0.2 ml saline flush. The pressor response in mm Hg was measured by the difference from pre-injection arterial pressure to the maximum pressure achieved. injection was repeated every 10 minutes until three consecutive injections yielded responses within 4 mmHg of each other. These three responses were then averaged and represented the control response to AII. The test compound was suspended in 0.5% methylcellulose in water and was administered by gavage. The volume administered was 2 ml/kg body weight. The standard dose was 3 mg/kg. Angiotensin II bolus injections were given at 30, 45, 60, 75, 120, 150, and 180 minutes after gavage. The pressor response to AII was measured at each time point. The rats were then returned to their cage for future testing. A minimum of 3 days was allowed between tests. Percent inhibition was calculated for each time point following gavage by the following formula: [(Control Response - Response at time point)/Control Response] X 100. Results are shown in Table III.

#### Assay "D": Renal Hypertensive Rat Model

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A combination therapy of an angiotensin II 25 receptor antagonist and an epoxy-steroidal aldosterone receptor antagonist may be evaluated for blood pressure lowering activity in the renal-artery ligated hypertensive rat, a model of high renin hypertension. In this model, six days after ligation of the left renal artery, both plasma renin activity and blood pressure are elevated significantly 30 [J.L. Cangiano et al, <u>J. Pharmacol. Exp. Ther.</u>, <u>206</u>, 310-313 (1979)]. Male Sprague-Dawley rats are instrumented with a radiotelemetry blood pressure transmitter for continuous monitoring of blood pressure. The rats are anesthetized with a mixture of ketamine-HCl (100 mg/kg) and acepromazine 35 maleate (2.2 mg/kg). The abdominal aorta is exposed via a midline incision. Microvascular clamps are placed on the

aorta distal to the renal arteries and at the iliac bifurcation. The aorta is punctured with a 22-guage needle and the tip of a catheter is introduced. The catheter, which is held in place by a ligature in the psoas muscle, is connected to a radiotelemetry blood pressure transmitter (Mini-Mitter Co., Inc., Sunriver, OR). The transmitter is placed in the peritoneal cavity and sutured to abdominal muscle upon closing of the incision. Rats are housed singly above a radiotelemetry receiver and are allowed standard rat chow and water ad libitum. At least 5 days are allowed for 10 recovery from surgery. Mean arterial pressure and heart rate are measured on a Compaq DeskPro 286 AT computer. Data are sampled for 10 seconds at 200-500 hz at 2.5 to 10 min intervals 24 hours per day. After collecting control data for 24 hours, the rats are anesthetized with methohexital 15 (30 mg/kg, i.p.) and supplemented as needed. A midline abdominal incision is made, approximately 2cm in length to expose the left kidney. The renal artery is separated from the vein near the aorta, with care taken not to traumatize 20 the vein. The artery is completely ligated with sterile 4-0 silk. The incision is closed by careful suturing of the muscle layer and skin. Six days later, when MAP is typically elevated by 50-70 mmHg, an AII receptor antagonist, or an aldosterone receptor antagonist, or a 25 combination of the two compounds are administered by gavage each day for about 8 weeks. Single drug dosing is carried out using 20 and 200 mg/kg/day of epoxymexrenone and 1,3,10,30 and 100 mg/kg/day of an AII receptor antagonist. Drug mixtures are obtained by administering a combination of 30 a dose of 1,3,10,30 or 100 mg/kg/day of the AII receptor antagonist with a dose of either 20 or 200 mg/kg/day of the aldosterone antagonist. Blood pressure lowering is monitored by the radiotelemetry system and responses with the compounds are compared to responses obtained in vehicletreated animals. Plasma and urinary sodium and potassium levels are monitored as a measure of the effectiveness of the aldosterone blockade. Urine samples are collected

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overnight using metabolic cages to isolate the samples. Plasma samples are obtained by venous catheterization. Sodium and potassium are measured by flame photometry. Cardiac fibrosis is determined by histological and chemical measurements of the excised hearts following perfusion fixation. Left and right ventricles are weighed, embedded and sectioned. Subsequently, sections are stained with picrosirius red and the red staining collagen areas are quantitated by computerized image analysis. The apex of the heart is acid digested and the free hydroxyproline measured colorimetrically. It is expected that MAP will be significantly lowered toward normal pressures in the test animals, treated with the combination therapy and that the condition of myocardial fibrosis will be arrested or avoided.

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TABLE III

In Vivo and In Vitro Angiotensin II

Activity of Compounds of the Invention

Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		<sup>3</sup> Assay C		
Compound	IC <sub>50</sub>	pA <sub>2</sub>	Dose	Inhibition	Duration	
Example #	(nM)		(mg/kg)	( %)	(min.)	
1	N.I.	NT	NT	NT	NT	
2	95	7.37/7.59	10	95	60	
			30	98	90-120	
3	5.4	$8.70 \pm 0.2$	10	50	>180	
			30	100	200+	
4	NT	NT	NT	NT	NT	
5	200	7.48/6.91	30	38	20-30	
6	1300	6.55/6.82	100	90	120	
7	84	8.01/8.05	30	90	130	
8	17,000	NT	NT	NT	NT	
9	700	6.67/6.12	30	80	75	
			100	100	130	
10	4.9	8.19/7.59	3	86	100	
			30	100	240	
11	160	6.45/6.77	NT	NT	NT	
12	6.0	8.66/8.59	NT	NT	NT	
13	17	8.70/8.85	NT	NT	· NT	
14	7.2	8.84/8.71	NT	NT	NT	
15	16	8.31/8.30	NT	NT	NT	
16	6.4	8.95/9.24	NT	NT	NT	
17	4.0	8.64/8.40	NT	NT	NT	
18	970	6.14/6.09	NT	NT ·	NT	
19	12,000	5.18/5.35	NT	NT	NT	

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Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		<sup>3</sup> Assa	y C
Compound	IC <sub>50</sub>	$pA_2$	Dose	Inhibition	Duration
Example #	(MM)	***	(ma/ka)	(%)	(min.)
20	78,000	5.89/5.99	100	10	45
21	87	7.71.7.21	NT	NT	NT
22	460	6.60/6.46	NT	NT .	NT
23	430	6.48/7.15	NT	NT	NT
24	10	7.56/7.73	NT	ТИ	NT
25	480	6.80/6.73	NT	NT	NT
26	3.2	9.83/9.66	10	50	>180
27	180	NT	NT	NT	NT
28	570	5.57/6.00	NT	NT	NT
29	160	NT ·	NT	NT	NT.
30	22	7.73/7.88	30	50	>180
31	14	NT	NT	NT	NT
32	16	7.68/7.29	NT	NT	NT
33	630	6.73/6.36	NT	NT	NT
34	640	5.34/5.69	NT	NT	NT
35	41	7.25/7.47	NT	NT	NT
36	1400	5.92/5.68	NT	NT	NT
37	340	6.90/6.85	NT	NT	NT
38	10	7.82/8.36	NT	NT	NT
39	10	7.88/7.84	NT	NT	NT
40	83	7.94/7.61	NT	NT	NT
41	3700	5.68/5.96	NT	NT	NT
42	370	6.56/6.26	NT	NT	NT
43	19	8.97/8.61	NT	NT	NT
44	16	8.23/7.70	NT	NT	NT
45	4.4	8.41/8.24	NT	NT ·	NT
46	110	6.80/6.64	NT	NT	NT

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	Test	<sup>1</sup> Assay A	2 <sub>Assay B</sub>		<sup>3</sup> Assay	7 C	
•	Compound	1C <sub>50</sub>	pA <sub>2</sub>	Dose	Inhibition	Duration	
	Example #	(nM)		(mg/kg)	( % )	(min.)	
5	47	21	7.85/7.58	NT	NT	NT	
	48	680	6.27/6.75	NT	NT	NT	
	49	120	7.06/7.07	NT	NT	NT	
	.50	54	7.71/7.89	NT	NT	NT	
	51	8.7	8.39/8.51	NT	NT	NT	
10	52	100	8.14/8.12	NT	NT	NT	
	53	65	7.56/7.83	NT	NT	NT	
	54	3100	6.02	NT	NT	NT	
	<b>55</b> ·	80	6.56/7.13	NT	NT	NT	
	56	5.0	9.04/8.35	NT	NT	NT	
15	57 .	2300	6.00	NT	NT	NT	
	58	140	6.45/6.57	NT	NT	NT	
	59	120	7.23/7.59	NT	NT	NT	
	60	2200	6.40/6.03	NT	NT	NT	
	61	110	7.29/7.70	NT	NT	NT	
20	62	26	8.69/8.61	NT .	NT	NT	
	63	61	7.77/7.67	NT	NT	NT	
	64	54	7.00/6.77	NT	NT	NT	
	65	23	7.85/7.75	NT	NT	NT	
	66	12	9.34/8.58	NT	NT	NT	
25	67	3100	5.88/5.78	NT	NT	NT	
	· 68	8.6	8.19/8.65	NT	NT	NT	
	69	15	7.80/8.28	NT	NT	NT	
	70	44	7.71/8.05	NT	NT	NT	
	71	12,000	*	NT	NT	NT	
30	72	83	6.11/6.10	NT	NT ·	NT	
	73	790	7.65/7.46	NT	NT	NT	

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	Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		<sup>3</sup> Assay	-
	Compound	1C <sub>50</sub>	pA <sub>2</sub>	Dose	Inhibition	Duration
	Example #	(MM)		(mg/kg)	(%)	(min.)
5	74	6.5	8.56/8.39	NT	NT	NT
	75	570	6.00/5.45	NT	NT	NT
	76	5400	5.52/5.78	NT	NT	NT
	77	15,000	5.77	NT	NT	NT
	78	101	7.0		93	60-100
10	79	4.9	9.2		100	>200
					50	>180
	80	25	8.1		NT	NT
	81	18	8.0		40	180
	82	7.9	8.5		20	180
15	83	3.6	8.3		15	>180
	84	16	7.1		20	30
	85	8.7	8.9		NT	NT
	86	9	7.8		NT	NT
	87	91	7.8		. NT	NT
20	88	50	7.7		NT	NT
	89	18	7.9		NT	NT
	90	5.6	9.0		NT	NT
	91	30	8.6		40	>180
	92	35	7.9		NT	NT
25	93	480	NT		NT	NT
	94	5,800	NT		NT	NT
	95	66	8.2		NT	NT
	96	21	8.0		NT	NT
	97	280	7.7		NT	NT
30	98	22	8.1		NT	NT
	99	280	6.5		NT	NT
	100	4.4	9.4		NT	NT
	101	36	7.8		NT	NT

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	Test	<sup>1</sup> Assay A	A <sup>2</sup> Assay B		<sup>3</sup> Assay	y C
	Compound	IC <sub>50</sub>	pA <sub>2</sub>	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
5	102	43	7.7		NT	NT
	103	12	8.0		NT	NT
	104	15	8.0		NT	NT
	105	290	6.6		NT	NT
	106	48	7.7		NT	NT
)	107 ,	180	8.3		NT	NT
	108	720	5.3	100	45	90
	109	250	7.3	30 .	50	30
	110	590	6.4		NT	NT
	111	45	9.0	30	87	160
5	112	2000	5.2		NT	NT
	113	12	8.4	10	60	180
	114	400	6.4		NT	
	115	11	8.2	3	40	>240
	116	230	6.5		NT	
)	117	170	6.5		NT	
	118	37	9.21/9.17	10	70	120
	119	16	9.21/9.00	3	20	60
	120	25	9.05/8.77	10	80	240
	121	46	NT		NT	
5	122	46	NT		NT	
	123	50	NT		NT	
	124	40	9.42/9.12	3	45	>180
	125	40	9.25/8.80	3	35	>240

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	Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		3 <sub>Assay</sub>	С
	Compound	IC <sub>50</sub>	$pA_2$	Dose	Inhibition	Duration
	Example #	(Mn)		(mg/kg)	(%)	(min.)
5	126	240	7.20/7.05		NT	
	127	12,000	4.96		NT	
	128	16	8.63/8.40		NT	
	129	6,700	5.30		NT	
	130	40	8.10/7.94		NT	
10	131	9.5	7.53/8.25			
	132	12	8.6		NT	
	133	10	8.7	3	20	180
			`			90-120
	134	22	9.3	3	35	180
15	135	16	8.5	3	35	>180
	136	NT	NT		NT	
	137	220	8.3		NT	
	138	130	8.2		NT	
	139	0.270	6.3		NT	
20	140	0.031	8.1		100	160
	141	0.110	8.02		. NT	NT
	142	2.000	NA		NT	NT.
	143	0.052	7.7	•	85	75
	144	0.088	7.7		50	125
25	145	0.480	6.7		NT	NT
	146	0.072	6.4		NT	NT

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	Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		<sup>3</sup> Assay	, C
	Compound	IC <sub>50</sub>	pA <sub>2</sub>	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
	147	5.8	5.6	3	74	5-10
5	148	0.87	5.8	3	92	20-30
	149	1.1	6.1	3	NT	NT
	150	14	8.03/7.80	3	25	>180
	151	17	7.76/7.97	3	15	180
	152	150	7.46/7.23	3	10	140
10	153 .	13	8.30/7.69	3	25	>180
	154	97	8.19/8.38		NA	<b>L</b>
	155	86	7.60/7.14		NA	<u>.</u>
	156	78	8.03/7.66		NA	<b>L</b>
	157	530 -	/6.22		NA	
15	158	54	8.23/8.14	3	30	>180
	159	21	7.92/7.56	3	10	150
	160	64	7.87/7.71			
	161	28			NA	i
	162	380	6.21/6.55		NA	
20	163	420	7.42/6.75		NA	
	164	1700			NА	
	165	410	6.90/7.18		NA	1

Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		<sup>3</sup> Assa	y C
Compound	1C <sub>50</sub>	$pA_2$	Dose	Inhibition	Duration
Example #	(nM)		(mg/kg)	. (8)	(min.)
166	160	7.57/7.74		N	'A
167	370	7.08/7.11		N	'A
168	420	7.69/7.58		N	'A
169	150	7.78/7.58	3	15	180
170	26	7.08/7.77	3	40	>180
171	28	7.52/7.11	3	0	0
172	70	7.15/7.04		N	Α
173	90	7.49/6.92		N	Α
174	180	7.29/7.02		N	Α
175	27	NA	3	0	0
176	9.8	7.69/7.55	3	10	150
177	26	7.41/7.85	3	15	180
178	88	7.54/7.47			Α
179	310	6.67/ -		N	A
180	20	7.56/7.15	3	25	180
181	21	7.70/7.12	3	20	180
182	59	NA		N	A
183	390	NA		N	A
184	1100	6.78/ -		N	A

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	Test	· 1 <sub>Assay A</sub>	2 <sub>Assay</sub> B		<sup>3</sup> Assa	уС
	Compound	IC <sub>50</sub>	$\mathtt{pA}_2$	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	( % )	(min.)
5	185	6.5	8.82/8.53	3	50	> 180
	186	38	8.13/7.40	3	25	180
	187	770	7.46/6.95		NA	
	188	140	7.72/7.09		NA	
٠	189	29	8.64/8.23		NA	
10	190	10	7.87/7.89	3	10	180
	19i	81	7.75/7.76	3	10	180
	192	140			NA	
	193	11	9.27/8.87	3	10	180
	194	47	7.64/7.35		NA	
15	195	34	8.44/8.03		NA	
	196	31	7.68/8.26		NA	
	197	14	8.03/8.60		NA	
	198	7.6	8.76/8.64	3	35	> 180
	199	10	8.79/8.85	3	60	> 180
20	200	20	8.42/8.77	3	45	> 180
	.201	17	8.78/8.63	3	10	180
	202	12	8.79/8.64	3	65	> 180
	203	9.2	8.43/8.36	3	- 50	> 180
	204	16	9.17/8.86	3	75	> 180
25	205	20	9.14/9.15	3	40	> 180
	206	5.4	8.75/8.89	3	30	> 180
	207	99	9.04/8.60		NA	
	208	22	9.19/8.69	3	50	> 180
	209	5.0	9.41/9.16	3	25	> 180
30	210	3.6	8.36/8.44	3	15	180
	211	18	8.74/8.67	3	35	> 180
	212	23	8.85/8.25	3	15	180
	213	51	NA		NA	
	214	65	NA .		NA	
35	215	45	NA		NA	
	216	5.4	8.80/9.04	3	50	> 180
					- •	, 100

Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		<sup>3</sup> Assa	уС
Compound	1C <sub>50</sub>	$pA_2$	Dose	Inhibition	Duration
Example #	(nM)		(ma/ka)	(%)	(min.)
217	9.4	NA	3	65	> 180
218	9.0	NA		N	A
219	14	NA		N	A
220	7.0	NA	3 ·	75	120
221	4.8	NA	3	25	> 180
222	5.0	NA		N	A
223	14	7.45/7.87	3	20	> 180
224	91	NA		N	A
225	160	NA		N	A
226	93	NA		N	A
227	89	7.55/7.67		N	A
228	4.5	9.17/8.25	3	80	>180
229	19	NT	3	40	>180
230	2.6	8.23/8.69	3	25	>180
231	3.6	NT	3	· 75	>180
232	4.4	8.59/8.89	3	70	>180
233	84	8.51/8.78		N	Т
234	5.0	8.49/9.00	3	20	_
235	34	7.14/7.07		N	Т
236	4.9	NC	3	70	>180
237	3.6	NT		N	T
238	1.7	NT	3	15	>180
239	6.8	7.88/8.01	3	20	>180
240	120	NA		N	A
241	6.9	8.57/8.24	3	40	>180
242	110	7.11/6.60		N	A
243	250	NA		N	A
244	150	7.17/7.17		N	A
245	98	6.64/7.04	•	N	A
246	72	7.46/7.59		И	A
247	9.4	8.26/8.41	3	20	180

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			200		·- ·- ·- ·- ·- ·- ·- ·- ·- ·- ·- ·- ·- ·	
	Test	<sup>1</sup> Assay A	<sup>2</sup> Assay B		3 <sub>Ass</sub>	ay C
	Compound	IC <sub>50</sub>	pA <sub>2</sub>	Dose	Inhibition	Duration
	Example #	(nM)		(mg/kg)	(%)	(min.)
	248	20	7.68/7.50	3	10	
5	249	4.4	NA	3	20	>180
	250	43	NA	3	0	
	251	25	NA		1	NA
	252	13	NA		1	NA
	253	2.6	'NA		1	NA AV
10	254	72	NA		ì	NΑ
	255	12	7.61/7.46	3	20	>180
	256	4.1	8.43/7.78	3	30	>180
	257	160	6.63/6.68		1	NΑ
	258	350	6.84/6.84		1	NΑ
15	259	54	NA		1	NA.
	260	220	NA		1	ΑV
	261	18	NA		1	JA.
	262	530	-/6.22		ì	Al
	263	57	NA		1	NA .
20	264	11	NA		ı	AA
	265	110	NA		1	NA.
	266	290	NA		ı	NA .
	267	25	NA	3	25	>180
	268	520	NA	3	0 .	
25	269	9.7	NA		1	IA.
	270	21	NA		7	NA .
	271	14	NC	3	20%	
	272	97	NC	3	70%	>180 min.
	273	9.8	8.53/8.61	3	25%	>180 min.
30	274	13	9.06/8.85	3	35%	>180 min.
	275	6.3	9.07/	3	40%	>180 min.
	276 ·	33	8.71/8.64	3	<20%	
	277	190	/6.54		<i>I</i> .	TT .
	278	30	8.49/8.51	3	50%	>180 min.
35	279	· 270	8.06/8.25		N	T
	280	480	6.41/6.35	NT	NT	NT

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NT = NOT TESTED

NC = Non-Competitive antagonist

\*Antagonist Activity not observed up to 10  $\mu\text{M}$  of test compound.

1Assay A: Angiotensin II Binding Activity

2Assay B: In Vitro Vascular Smooth Muscle Response

3Assay C: In Vivo Pressor Response

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Test Compounds administered intragastrically, except for compounds of examples #1-#2, #4-#25, #27-#29, #30-#79, #108-#109, #111, #118 and #139-#149 which were given intraduodenally.

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PCT/US96/08709

Administration of the angiotensin II receptor antagonist and the aldosterone receptor antagonist may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropyl-methyl cellulose, together with one or more of a lubricant, preservative, surface-active or dispersing agent.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical 20 composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of each active 25 ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.01 to 30 mg/kg body weight, particularly from about 1 to 15 mg/kg body weight, 30 may be appropriate.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose of each active component is from about 0.01 to 15 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred

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daily dose would be from about 1 to 10 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 15 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 15 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 10 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active. compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

In combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 5 mg to about 400 mg, and the AII antagonist may be present in an amount in a range from about 1 mg to about 800 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 400:1 to about 1:160.

In a preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 10 mg to about 200 mg, and the AII antagonist may be present in an amount in a range from about 5 mg to about 600 mg, which represents aldosterone
antagonist-to-AII antagonist ratios ranging from about 40:1 to about 1:60.

In a more preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 20 mg to about 100 mg, and the AII antagonist may be present in an amount in a range from about 10 mg to about 400 mg, which represents aldosterone

antagonist-to-AII antagonist ratios ranging from about 10:1 to about 1:20.

The dosage regimen for treating a disease

5 condition with the combination therapy of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the active components of this combination therapy invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the 15 components may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric 20 acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for 25 parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations 30 for oral administration. The components may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and 35 modes of administration are well and widely known in the pharmaceutical art.

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Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

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### What Is Claimed Is:

1. A method to treat a subject susceptible to or afflicted with cardiofibrosis or cardiac hypertrophy, which method comprises administering a combination of drug agents comprising a therapeutically-effective amount of an angiotensin II receptor antagonist and a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist.

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- 2. The method of Claim 1 wherein said epoxysteroidal aldosterone receptor antagonist is selected from epoxy-containing compounds.
- 3. The method of Claim 2 wherein said epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroidal nucleus of a 20-spiroxane compound.
- 4. The method of Claim 3 wherein said 20- spiroxane compound is characterized by the presence of a  $9\alpha$ -,11 $\alpha$ -substituted epoxy moiety.
- 5. The method of Claim 2 wherein said epoxycontaining compound is selected from the group consisting 25 of

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, $\gamma$ -lactone, methyl ester,  $(7\alpha,11\alpha,17\alpha)$ -;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester,  $(7\alpha,11\alpha,17\alpha)$ -;

3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ 35 lactone,(6 $\beta$ ,7 $\beta$ ,11 $\beta$ ,17 $\beta$ )-;

pregn-4-ene-7,21-dicarboxylic acid,9,11-

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epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt,  $(7\alpha,11\alpha,17\alpha)$ -;

pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-17-hydroxy-3-oxo-,7-methyl ester, monopotassium salt,  $(7\alpha,11\alpha,17\alpha)$ -;

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3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ -lactone(6 $\alpha$ ,7 $\alpha$ ,11. $\alpha$ )-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester,  $(6\alpha,7\alpha,11\alpha,17\alpha)$ -;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt,  $(6\alpha,7\alpha,11\alpha,17\alpha)$ -;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ -lactone, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ .,17 $\alpha$ )-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-25 17-hydroxy-3-oxo-, $\gamma$ -lactone, ethyl ester,  $(7\alpha,11\alpha,17\alpha)$ -; and

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, $\gamma$ -lactone, 1-methylethyl ester, $(7\alpha,11\alpha,17\alpha)$ -.

6. The method of Claim 1 wherein said angiotensin II receptor antagonist is selected from compounds consisting of a first portion and a second portion, wherein said first portion is selected from a fragment of Formula I:

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Ar-Alk-L

Ar-L-Ar-Alk-L

Het-L-Ar-Alk-L

Het-L-Het-Alk-L

(I)

Ar-L-Het-Alk-L

Het-L-Alk-L

wherein Ar is a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being fully unsaturated or partially or fully saturated;

wherein Het is a monocyclic or bicyclic fused ring system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from one or more hetero atoms selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members;

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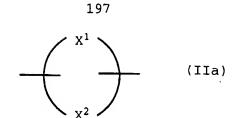
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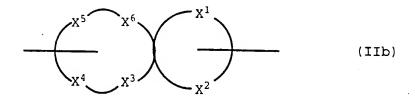
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wherein Alk is an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms;

25. wherein L is a straight bond or a bivalent linker moiety selected from carbon, oxygen and sulfur;

and wherein said second portion is a monocyclic heterocyclic moiety selected from moieties of Formula IIa or is a bicyclic heterocyclic moiety selected from moieties of Formula IIb:





wherein each of X<sup>1</sup> through X<sup>6</sup> is selected from -CH=,
-CH2-, -N=, -NH-, 0, and S, with the proviso that at

least one of X<sup>1</sup> through X<sup>6</sup> in each of Formula IIa and
Formula IIb must be a hetero atom, and wherein said
heterocyclic moiety of Formula IIa or IIb may be attached
through a bond from any ring member of the Formula IIa or
IIb heterocyclic moiety having a substitutable or a bondforming position.

7. The method of Claim 6 wherein said monocyclic heterocyclic moiety of Formula IIa is selected from thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-

pyranyl, 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl,
pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, vtriazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

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oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl, 1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

- 8. The method of Claim 7 wherein said bicyclic heterocyclic moiety of Formula IIb is selected from benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, 10 isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2Hfuro[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-15 pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiolo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 20 4H-1,3-dioxolo[4,5-d]imidazolyl.
  - 9. The method of Claim 8 wherein said angiotensin II receptor antagonist compound having said first-and-second-portion moieties of Formula I and II is further characterized by having an acidic moiety attached to either of said first-and-second-portion moieties.
- 10. The method of Claim 9 wherein said acidic moiety is attached to the first-portion moiety of Formula 30 I and is defined by Formula III:

 $-U_nA$  (III)

wherein n is a number selected from zero through three,
inclusive, and wherein A is an acidic group selected to
contain at least one acidic hydrogen atom, and the amide,
ester and salt derivatives of said acidic moieties;

wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

11. The method of Claim 10 wherein said acidic moiety is selected from carboxyl moiety and tetrazolyl moiety.

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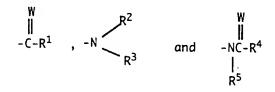
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of the formula

i

k

12. The method of Claim 10 wherein any of the moieties of Formula I and Formula II may be substituted at any substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, 20 carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals 25



30 wherein W is oxygen atom or sulfur atom; wherein each of  ${\bf R}^1$  through  ${\bf R}^5$  is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR6 and

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wherein Y is selected from oxygen atom and sulfur atom and R<sup>6</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkyl, aralkyl and aryl; wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is further independently selected from amino and amido radicals of the formula

$$-N \underbrace{ \begin{array}{c} R^9 \\ R^{10} \end{array}, \quad \begin{array}{c} W \\ -CN \\ R^{12} \end{array} \quad \text{and} \quad \begin{array}{c} W \\ \parallel \\ -NC-R^{13} \\ \parallel \\ R^{14} \end{array} }$$

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wherein W is oxygen atom or sulfur atom; wherein each of  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of  $\mathbb{R}^2$  and  $\mathbb{R}^3$  taken together and each of  $R^4$  and  $R^5$  taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and wnich heterocyclic group may be saturated or partially unsaturated; wherein each of  $R^2$  and  $R^3$  taken together and each of  $R^7$  and  $R^8$  taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido

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radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

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1.

- 13. The method of Claim 12 wherein said angiotensin II receptor antagonist is  $5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor antagonist is <math display="block">9\alpha-,11\alpha-\text{epoxy}-7\alpha-\text{methoxycarbonyl}-20-\text{spirox}-4-\text{ene}-3,21-\text{dione or a pharmaceutically-acceptable salt thereof.}$
- 14. The method of Claim 13 further characterized by said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about twenty-to-one of said angiotensin II receptor antagonist to said aldosterone receptor antagonist.
  - 15. The method of Claim 14 wherein said weight ratio range is from about five-to-one to about fifteen-to-one.
  - 16. The method of Claim 15 wherein said weight ratio range is about ten-to-one.
- 30 17. The method of Claim 1 wherein said angiotensin II receptor antagonist is selected from the group consisting of: saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, 35 BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22.

WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017,

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18. The method of Claim 17 wherein said angiotensin II receptor antagonist is selected from the group consisting of:

LY-301875, XH-148, XR-510, zolasartan and PD-123319.

- saralasin acetate, candesartan cilexetil, CGP-63170,
  20 EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,
  BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,
  EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,
  LY-235656, PD-150304, U-96849, U-97018, UP-275-22,
  WAY-126227, WK-1492.2K, YM-31472, losartan potassium,
- E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007 and PD-123177.
- 30 19. The method of Claim 1 comprising administering said combination to treat or prevent the progression of cardiofibrosis.
- 20. The method of Claim 1 comprising
  35 administering said combination to treat or prevent the progression of cardiac hypertrophy.

## **PCT**

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### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: METHOD TO TREAT CARDIOFIBROSIS WITH A COMBINATION THERAPY OF AN ANGIOTENSIN II ANTAGONIST AND AN EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST

#### (57) Abstract

A therapeutic method is described for treating cardiofibrosis or cardiac hypertrophy using a combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of a 9a,11asubstituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.

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### INTERNATIONAL SEARCH REPORT

rional Application No

PCT/US 96/08709 A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K31/585 A61K45/06 A61K31/41 //(A61K45/06,31:585). (A61K45/06, 31:41)According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category ' Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. WO,A,94 09778 (MERCK & CO LTD) 11 May 1994 1-20 see page 1-2; figures I-XI A see page 6, line 9; claims 1-3,5-8,10 14-16 WO, A, 91 15206 (DU PONT DE NEMOURS; MERCK & 1-20 CO) 17 October 1991 Α see page 21, line 12-20; claims 1-4,6-8 14 see page 24, line 7-12 see page 24, line 19-30 see page 26, line 1-6 EP,A,0 481 448 (SQUIBB & SONS INC.) 22 1-20 April 1992 Α see page 11, line 20-45; claims 13,17,18 1,6-8,12,13; examples 12-21 -/--X Further documents are listed in the continuation of box C. Patent family members are listed in annex. X Special categories of cited documents: T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled "O" document referring to an oral disclosure, use, exhibition or \*P\* document published prior to the international filing date but later than the priority date claimed \*& document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 21 November 1996 0 6, 12, 96

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Kanbier, D

## INTERNATIONAL SEARCH REPORT

Int tonal Application No PCT/US 96/08709

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		1984 see page 3, paragraph 5 - page 5, paragraph 4; claims 1-8,10 see page 21, paragraph 2 - page 22.	1-5

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International application No.

### INTERNATIONAL SEARCH REPORT

PCT/US 96/08709

Box I Observations where certain claims were found unsearchable (Continuation of item I of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  Remark: Although claim(s) 1-20  is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.  2. X Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:  Please see next page
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the large number of compounds, which are defined by the general formula/description, used in claims 2, 6-12, 17, 18, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application ( see Guidelines, part B, chapter III, paragraph 3.6).

A compound cannot be sufficiently characterized by its pharmacological profile or its mechanism of action as it is done in claim 1 as: "angiotensin II receptor antagonist" and a "aldosterone receptor antagonist". The search has been executed based on compounds specifically mentioned in claims 3-5, 13 and in the examples

Claims searched incompletely: 1, 2, 6-12, 17, 18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int rional Application No PCT/US 96/08709

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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WO-A-9115206	17-10-91	NONE		
EP-A-481448	22-04-92	CA-A- JP-A- US-A-	2053148 4330065 5470975	17-04-92 18-11-92 28-11-95
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